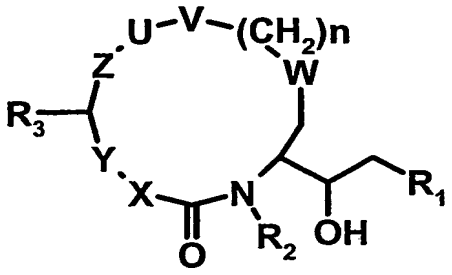
Claims

1. A compound of the formula



(I),

in which

R_1 is $CH(R_e)C(=O)N(R_a)R_b$ or $(CH_2)_kN(R_c)R_d$, wherein

k is 0, 1 or 2;

R_a and R_b, independently, are hydrogen or an optionally substituted (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, aryl, aryl(C_{1-4})alkyl, heteroaryl or heteroaryl(C_{1-4})alkyl group,

R_c and R_d, independently, are hydrogen or an optionally substituted (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, aryl, aryl(C_{1-4})alkyl, heteroaryl, heteroaryl(C_{1-4})alkyl, chroman-4-yl, isochroman-4-yl, thiochroman-4-yl, isothiochroman-4-yl, 1,1-dioxo-1lambda*6*-thiochroman-4-yl, 2,2-dioxo-2lambda*6*-isothiochroman-4-yl, 1,2,3,4-tetrahydro-quinolin-4-yl, 1,2,3,4-tetrahydro-isoquinolin-4-yl, 1,2,3,4-tetrahydro-naphthalen-1-yl, 1,1-dioxo-1,2,3,4-tetrahydro-1lambda*6*-benzo[e][1,2]thiazin-4-yl, 2,2-dioxo-1,2,3,4-tetrahydro-2lambda*6*-benzo[c][1,2]thiazin-4-yl, 1,1-dioxo-3,4-dihydro-1H-1lambda*6*-benzo[c][1,2]oxathiin-4-yl, 2,2-dioxo-3,4-dihydro-2H-2lambda*6*-benzo[e][1,2]oxathiin-4-yl, 2,3,4,5-tetrahydro-benzo[b]oxepin-5-yl or 1,3,4,5-tetrahydro-benzo[c]oxepin-5-yl group, or

R_a and R_b, or R_c and R_d, together with the nitrogen to which they are attached, form an optionally substituted pyrrolidinyl, 1-piperidinyl, 4-morpholinyl or piperazinyl group; and

R_e is optionally substituted (C_{1-8})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl(C_{1-4})alkyl;

R_2 is hydrogen or (C_{1-4})alkyl;

R_3 is hydrogen, (C_{1-6})alkyl or an optionally substituted (C_{1-8})alkylOC(=O)NH, (C_{3-7})cycloalkylOC(=O)NH, (C_{3-7})cycloalkyl(C_{1-4})alkylOC(=O)NH, aryl(C_{1-4})alkylOC(=O)NH, heteroaryl(C_{1-4})alkylOC(=O)NH, (C_{1-4})alkylC(=O)NH, (C_{3-7})cycloalkylC(=O)NH,

arylC(=O)NH, aryl(C_{1-4})alkylC(=O)NH, heteroarylC(=O)NH or heteroaryl(C_{1-4})alkylC(=O)NH group;

U is a bond, CF_2, CF_2CF_2, CHF, CHFCHF, cycloprop-1,2-ylene, (C_{1-3})alkylenoxy, (C_{1-8})alkylene, NR_g or an aromatic or heteroaromatic ring, which ring is optionally substituted with halogen, (C_{1-4})alkoxy, hydroxy or (C_{1-4})alkyl, whereby Z and V are in ortho- or meta-position to each other, wherein
R_g is hydrogen, (C_{1-8})alkyl or (C_{3-7})cycloalkyl;

V is CH=CH, cycloprop-1,2-ylene, $CH_2CH(OH)$, $CH(OH)CH_2$ or $CR_hR_hCR_hR_h$, wherein each R_h, independently, is hydrogen, fluorine or (C_{1-4})alkyl;

W is (C_{1-6})alkylene, O, S, $S(=O)_2$, C(=O), C(=O)O, OC(=O), $N(R_f)C(=O)$, $C(=O)NR_f$ or NR_f, wherein
R_f is hydrogen or (C_{1-4})alkyl;

X is an optionally substituted (C_{1-4})alkanylylidene, (C_{1-4})alkylene, (C_{3-7})cycloalkylene, piperidin-diyl, pyrrolidin-diyl, benzothiazole-4,6-diyl, benzoxazole-4,6-diyl, 1H-benzotriazole-4,6-diyl, imidazo[1,2-a]pyridine-6,8-diyl, benzo[1,2,5]oxadiazole-4,6-diyl, benzo[1,2,5]thiadiazole-4,6-diyl, 1H-indole-5,7-diyl, 1H-indole-4,6-diyl, 1H-benzimidazole-4,6-diyl or 1H-indazole-1,6-diyl group or an optionally substituted aromatic or heteroaromatic ring, whereby Y and $C(=O)NR_2$ are in meta-position to each other;

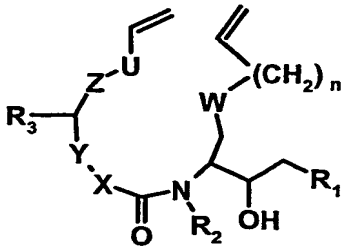
Y is a bond, O, $S(=O)_2$, $S(=O)_2NR_g$, $N(R_g)S(=O)_2$, NR_g, $C(R_g)OH$, $C(=O)NR_g$, $N(R_g)C(=O)$, $C(=O)N(R_g)O$ or $ON(R_g)C(=O)$, wherein
R_g is hydrogen, (C_{1-8})alkyl or (C_{3-7})cycloalkyl;

Z is O, CH_2, CF_2, CHF, cycloprop-1,2-ylene or a bond; and

n is 0 to 5,

the number of ring atoms included in the macrocyclic ring being 14, 15, 16 or 17,
in free base form or in acid addition salt form.

2. A process for the preparation of a compound as defined in claim 1 of the formula I, in free base form or in acid addition salt form, comprising the steps of cyclisation by metathesis of a compound of the formula



(II),

in which R_1, R_2, R_3, U, W, X, Y, Z and n are as defined for the formula I, in the presence of a catalyst, for instance a ruthenium, tungsten or molybdenum complex, optionally followed by reduction, oxidation or functionalisation of the resulting carbon-carbon-double bond, and of recovering the so obtainable compound of the formula I in free base form or in acid addition salt form.

3. A compound according to claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

4. A compound according to claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, for use in the treatment of neurological or vascular disorders related to beta-amyloid generation and/or aggregation.

5. A pharmaceutical composition comprising a compound as claimed in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, as active ingredient and a pharmaceutical carrier or diluent.

6. The use of a compound as claimed in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the treatment of neurological or vascular disorders related to beta-amyloid generation and/or aggregation.

7. The use of a compound as claimed in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of neurological or vascular disorders related to beta-amyloid generation and/or aggregation.

8. A method for the treatment of neurological or vascular disorders related to beta-amyloid generation and/or aggregation in a subject in need of such treatment, which comprises

administering to such subject a therapeutically effective amount of a compound as claimed in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form.

9. A combination comprising a therapeutically effective amount of a compound as claimed in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, and a second drug substance, for simultaneous or sequential administration.